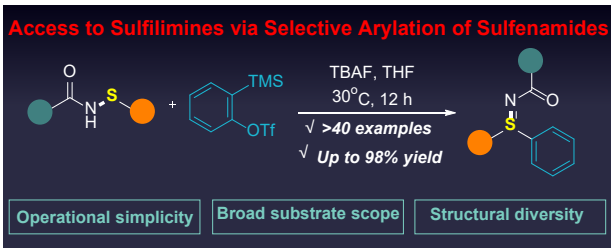
Selective S-arylation of Sulfenamides with Arynes: Facile Access to Sulfilimines

Yifeng Guo, Zhe Zhuang,‡ Xiaoying Feng,‡ Quanyu Ma, Ningning Li, Chaochao Jin, Hiroto Yoshida,* Jiajing Tan*

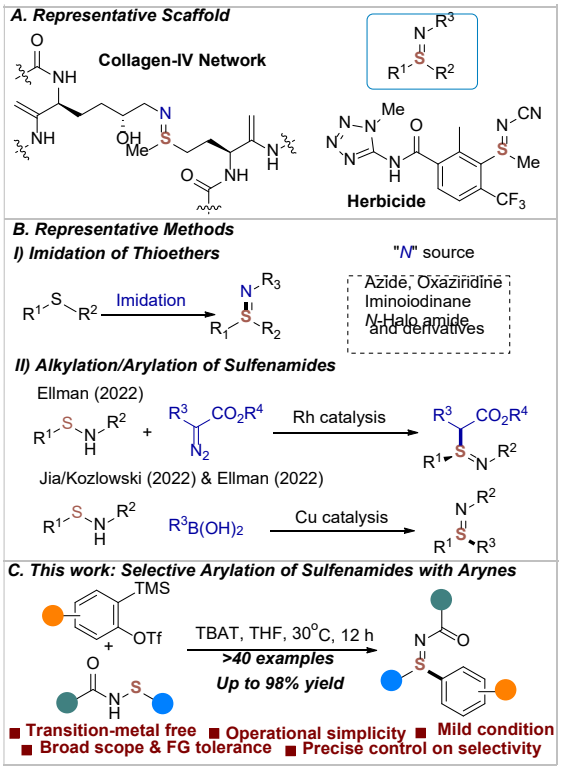


ABSTRACT: Sulfilimines, the aza-analogues of sulfoxides, are of increasing interests in medicinal and agrochemical research programs. However, the development of efficient routes for their synthesis remains relatively unexplored. In this study, we report a transition metal-free, selective *S*-arylation reaction between sulfenamides and arynes, enabling the facile preparation of structurally diverse sulfilimines under mild and redox-neutral condition in good yields. The application value of our method was further demonstrated by scale-up synthesis, downstream derivatization, and robustness screen.

Sulfilimines, the aza-analogues of sulfoxides, have gained significant attention from the synthetic community.[1] As a unique class of tetravalent sulfur(IV) compounds, they find widespread applications as ligands for catalysis, nitrene/*N*-radical reservoirs, drug/agrochemical candidates, and bioconjugation toolkits (Scheme 1A).[2] For instance, the groundbreaking work of Hudson and colleagues demonstrated that the sulfilimine motif can be employed to covalently cross-link hydroxylysine-211 and methionine-93 in collagen IV, which marked the first identification of sulfilimine motif in biomolecules.[3] More importantly, sulfilimines can be easily transformed to sulfoximines and sulfondiimines, which have emerged as important bioisosteres for drug and agrochemical discovery.[4] The resulting anticipation of increased sophistication in the recognition and design of such functional mimetics has stimulated efforts on developing the synthesis and incorporation of sulfilimines and their derivatives, which shall provide enhanced coverage of both chemical and intellectual property space.[5]

Nonetheless, the synthetic accessibility of sulfilimines, compared to their S-O counterparts, has been relatively limited, impeding their application in multiple research fields. The state-of-the-art methods predominantly relied on the direct imidation of thioethers using different imidating reagents, which suffered from the use of hazardous reagents/transition metals, limited substrate scope, and cumbersome operation (Scheme 1B).[6] New disconnection strategy for preparing such compelling targets has also witnessed rapid progress.[7] For instance, Ellman and co-workers detailed a Rh-catalyzed asymmetric *S*-alkylation reaction of *N*-acyl sulfenamides with diazo compounds.[8] In

Scheme 1. Background Introduction



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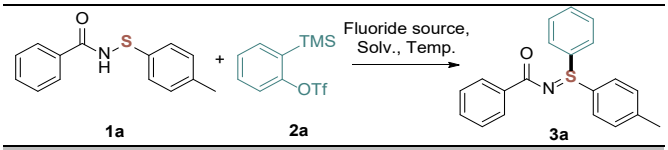
spired by this pioneering strategy involving C-S bond formation, the Jia/Kozlowski and Ellman group independently accomplished the Chan-Lam coupling reaction of sulfenamides with arylboronic acids, both of which demonstrated the crucial role of the *N*-carbonyl groups to modulate the chemoselectivity through chelation.[9] More recently, the direct electrophilic alkylation/arylation of sulfenamides was also disclosed.[10] Although these significant advancements have shown certain synthetic appeal, the development of new complementary synthetic strategies for sulfilimines remains an urgent task in order to meet their growing utility while overcoming the aforementioned synthetic limitations.

Aryne chemistry has garnered significant attention in recent years as a means to rapidly expand chemical space and even facilitate the synthesis of medicinally relevant compounds.[11] Thanks to the discovery of silyl triflate type precursor, the aryne chemistry has witnessed the renaissance, leading to the development of numerous novel transformations.[12] These unique synthetic methods often feature mild conditions, avoidance of transition metals and operational simplicity, thereby allowing the build of molecular complexity in high efficacy. Given our long-standing interests in the combination of aryne species with organosulfur compounds, we naturally questioned whether the polarizable aryne species with low-lying LUMO could exhibit sufficient "soft" electrophilic character to pair the reactivity with the "soft" sulfur center, thus empowering the chemoselective *S*-arylation.[13] Although the tentative pathway was proposed on basis of insight gained from our previous thioimidate project, we still anticipated several associated challenges within it.[13a] For instance, the N-S bond might be vulnerable for breaking (homolysis), while Biju *et al* previously disclosed the insertion reactivity of N-S bond with aryne (heterolysis).[14] Thus, another critical task would be the identification and manipulation of the *N*-protection group to achieve the selectivity control. Despite these challenges, we are excited to present our recent research efforts on developing a mild and redox-neutral *S*-arylation reaction between sulfenamides and arynes (Scheme 1C). This transition metal-free protocol offers complete site-selectivity control, allowing for the rapid access to a broad range of sulfilimine and en route to medicinally relavatnt S(IV) motifs.

The reaction discovery and optimization commenced by identifying a suitable aryne induced condition by employing *N*-(*p*-tolylthio)benzamide (**1a**) and *o*-(trimethylsilyl)phenyl triflates (**2a**) as the model substrates. To our delight, the quick screening of a range of fluoride-based initiation conditions demonstrated that TBAF in THF gave the optimal yield of **3a** (Table 1, entry 4 *vs*. entries 1-5). More importantly, the inspired choice of benzoyl group effectively modulated the reactivity of sulfenamides with complete control on *S*-arylation. Both lowering or raising the reaction temperature resulted in a decrease in the reaction yield (entries 6-7). Reducing the amount of TBAF to 1.5 equivalent, the product could still be formed in 94% yield (entry 8). Finally, varying the concentration or the reagent ratio also afforded the desired product with comparable yields (entries 9-10).

Table 1. Reaction Condition Optimization[a]



1a 2a 3a

Entry	"F-" source	Solvent	Temp. (°C)	Yield[b] (%)
1	KF/18-C-6	THF	30	93
2	CsF	ACN	30	73
3	Cs_2CO_3/18-C-6	THF	30	81
4	TBAF	THF	30	96(94[c])
5	TBAT	THF	30	95
6	TBAF	THF	0	63
7	TBAF	THF	40	92
8[d]	TBAF	THF	30	94
9	TBAF	THF[e]	30	95
10[f]	TBAF	THF	30	89

[a]**1a** (0.2 mmol), **2a** (0.3 mmol), "F-"source (0.5 mmol), solvent (1.5 ml), N_2. [b]Determined by ^{1}H-NMR using CH_2Br_2 as the internal standard. [c]Isolated yield. [d]TBAF (0.3 mmol). [e]THF (1.0 ml). [f]**1a:2a** = 1:1

With optimal reaction conditions in hands, we next evaluated the scope of sulfenamides. As depicted in Scheme 2, the reactions of versatile *N*-aroyl sulfenamides all proceeded smoothly to deliver the target products (**3a-3l**) in moderate to good yields, regardless of their functional groups as well as substitution patterns. Indeed, the bromo-substitution could serve as the latent synthetic handle for further elaborations.[15] Additionally, investigations on varying the *S*-aryl and *S*-alkyl structural units of sulfenamides were explored, and the arylated products (**3k-3r**) were readily accessed in moderate to good yields. Next, we assessed the applicability of current method with respect to the substitution group on the nitrogen atom, and found that polyaromatic, cinnamyl, heteroaromatic and aliphatic groups all proved to be viable. To our delight, Boc-, Cbz- and Ts-protected sulfenamide were amenable to give **3x**, **3y** and **3z** in 90%, 92% and 82% yield, respectively. Noteworthy, the proline-derived substrate with enolizable α-proton also underwent the arylation smoothly to afford **3aa** in 50% yield with 2:1 d.r.

The generality of our protocol for substituted Kobayashi precursors were then explored (Scheme 2, part B). A series of symmetrical arynes all undertook the title reaction smoothly, leading to **4a-4e** in moderate-to-good yields. In accordance with the distortion/interaction model,[16] the employment of 3-methoxy-substituted benzyne delivered a single regioisomer **4f** in 58% yield. For other unsymmetrical arynes, the desired products (**4g-4i**) were also successfully obtained in good overall yields albeit with less-satisfying regioselectivities, which was consistent with the weak-biasing effects disclosed in earlier reports.[17] Moreover, silyl aryl triflate derived from the estrone was readily converted to **4j+4j'** in 93% yield, showcasing relevance of

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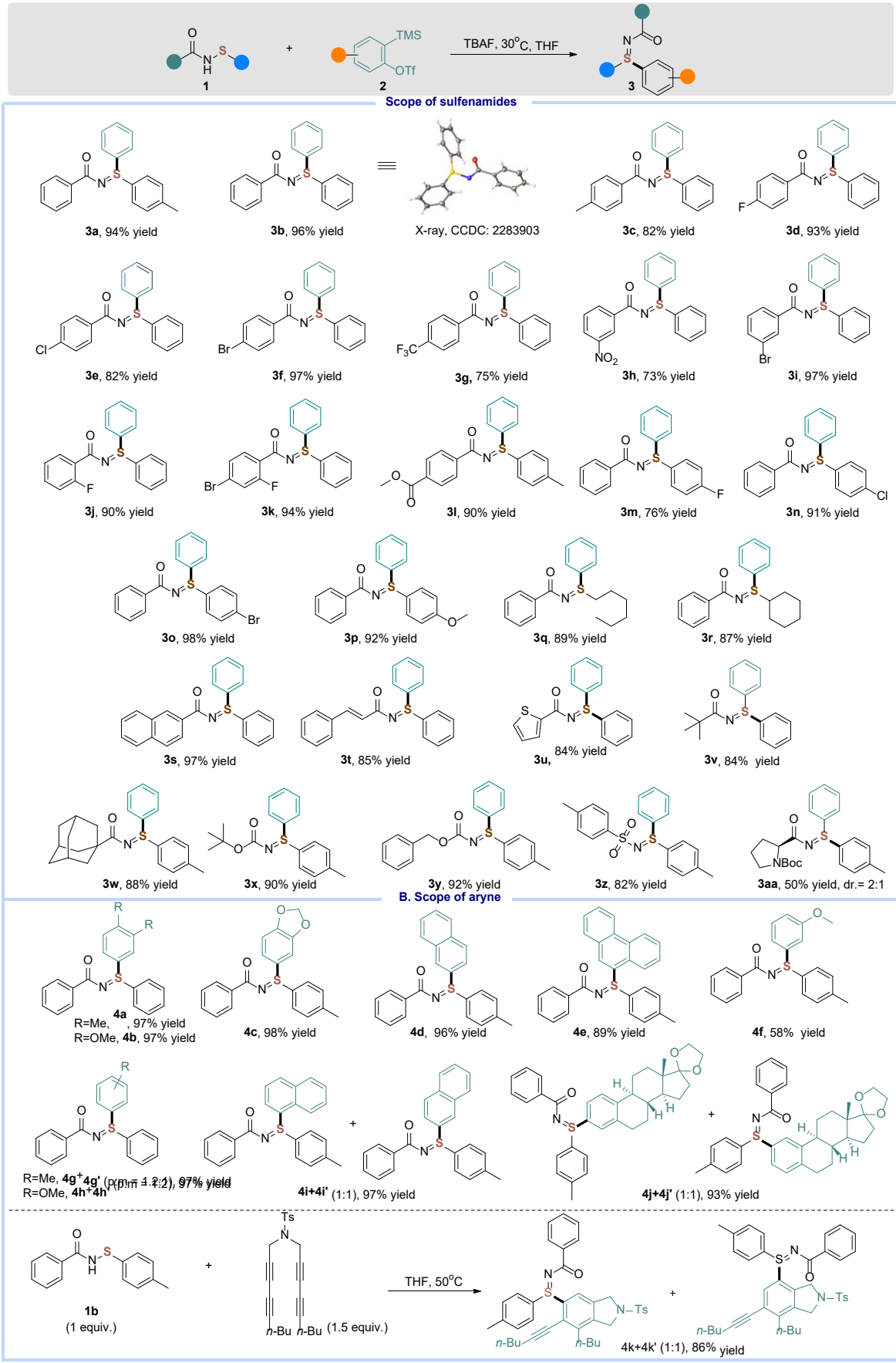
Scheme 2. Substrate Scope[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), TBAF (0.5 mmol), THF (1.5 ml), N_2, 12 hours.

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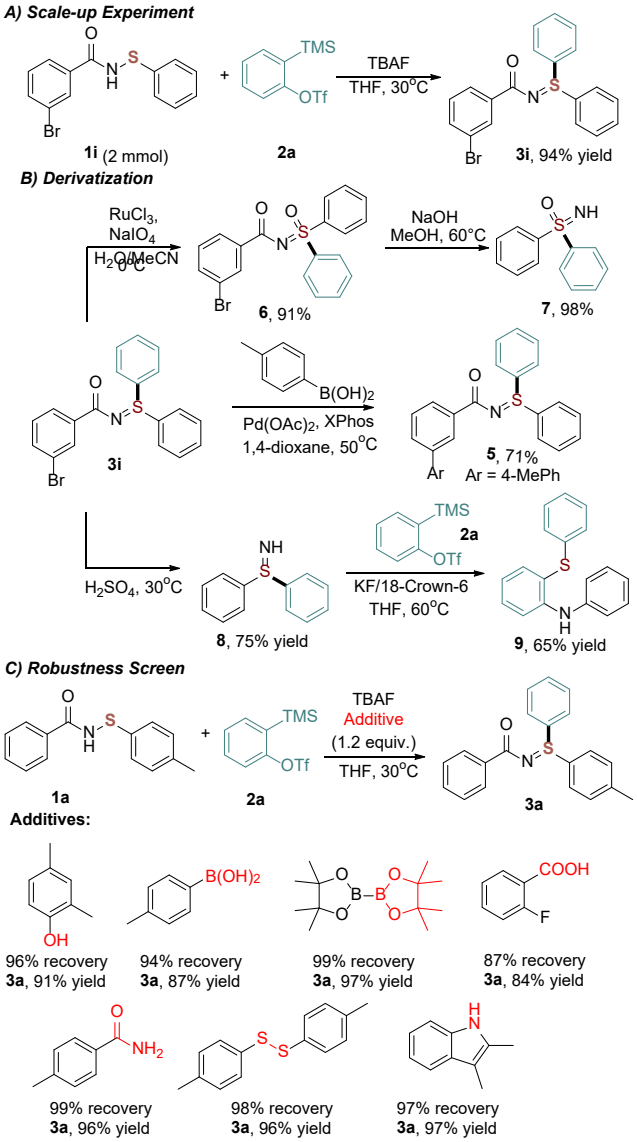
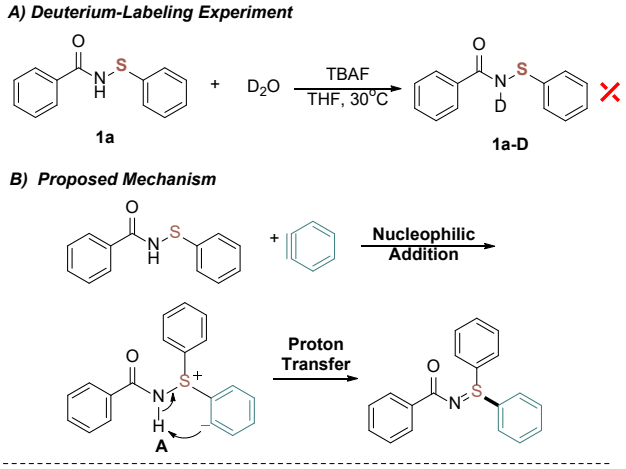
the methodology to incorporate the sulfilimine to biologically active compounds. Further investigation to gain insights into the reactivity of other type of aryne precursors were performed. When **1a** was reacted with aryne that was thermally generated by hexadehydro-Diels-Alder (HDDA) reaction, the arylation products (**4k+4k'**) were obtained in a combined 86% yield under base-free conditions, which should offer additional synthetic flexibility of our protocol (For details on other aryne precursors, please see the ESI).

Scheme 3. Synthetic Applications.



To demonstrate the synthetic utility, the scale-up reaction was conducted under standard conditions, affording **3i** in same level of isolated yields (Scheme 3, part A). Next, we sought to present the downstream derivatization of sulfilimines products (part B). The exemplificative arylation product **3i** underwent the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction with *p*-tolylboronic acid successfully to afford the biaryl product **5** in a 71% isolated yield. We also managed to convert **3i** to sulfoximine **6** in 91% yield in the presence of $RuCl_3$ and $NaIO_4$. Treatment of **6** with sodium hydroxide furnished the *NH*-sulfoximine **7** in a 98% isolated yield. The hydrolysis of **3i** with sulfuric acid furnished the *NH*-diphenyl sulfilimine **8** in 75% yield, which could further underwent insertion reaction with arynes to afford *ortho N,S*-difunctionalization product in 65% yield. Finally, an additive-based robustness screen was performed in the presence of excess amounts of additives under otherwise identical conditions. In all cases, **3a** was obtained in similar level of yields and with the additives mostly recovered, further suggesting that our protocol be potentially well-suited for highly functionalized "real-world" substrates in pharmaceutical or agrochemical research projects.

Scheme 4 Reaction Mechanism



The control experiment using heavy water suggested no incorporation of deuterium to the substrate in the presence of TBAF in THF, which might provide evidence to support the direct S-arylation pathway. On basis of the finding along with literature precedence,[11-13] a tentative mechanism was proposed, as shown in Scheme 4. Firstly, the nucleophilic addition of *N*-(phenylthio)benzamide to *in-situ* formed aryne species led to the key sulfonium zwitterion intermediates **A**.[18] Next, the rapid proton transfer yielded the final sulfilimine product.

In summary, we have herein successfully developed a facile synthesis of sulfilimines through the chemoselective sulfur arylation of sulfenamides using readily available aryne species. This operational simple protocol demonstrates good yields and high compatibility with a wide range of functional groups under mild and transition metal-free conditions. The key to our success lies in the strategic use of *N*-acyl substitution to modulate the reactivity of sulfenamides. The synthetic utility of this method was further demonstrated through the scale-up experiment, downstream derivatizations toward versatile sulfur-containing building blocks, and additive-based robustness screen. It's our hope that this method will provide a powerful alternative for the synthesis of sulfenamides and accelerate the discovery of new bioactive sulfur(IV) motifs.

ASSOCIATED CONTENT

Supporting Information

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The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectroscopic data (PDF)

AUTHOR INFORMATION

Corresponding Author

Jiajing Tan - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*; orcid.org/0000-0003-3825-9344; Email: tanjj @mail.buct.edu.cn.
Hiroto Yoshida - *Graduate School of Advanced Science and Engineering, Hiroshima University, Higashi-Hiroshima 739-8526, Japan.*; orcid.org/ 0000-0001-6890-4397; Email: yhiroto@hiroshima-u.ac.jp.

Author

Yifeng Guo - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*
Zhe Zhuang - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*.
Xiaoying Feng - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*.
Quanyu Ma - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*.
Ningning Li - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*.
Chaochao Jin - *College of Chemistry, Beijing University of Chemical Technology (BUCT), Beijing 100029, China*.

Notes

The authors declare no competing financial interest.

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